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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/623,176	07/18/2003	Elsa A.J.M. Goulmy	2183-6047US	4726

24247 7590 07/08/2005

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EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/623,176	GOULMY ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *April 14, 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *1-6,10,11,20-23,25-29,32-34,37-44,47 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9,12-19,24,30,31,35,36,45,46,49 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/18/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response received April 14, 2005 is acknowledged.

Claims 8, 9, 12-20, 24, 31-32, 35, 36, 44-46 have been amended.

Claims 49 and 50 have been added.

Claims 1-50 are currently pending in the application.

Applicant's election without traverse of Group 3, drawn to methods of inducing tolerance by administering the peptide of SEQ ID NO:1, claim 7 and as amended claims 8, 9, 12-19, 24, 30, 31, 35, 36, 45, 46, 49, and 50 in the reply filed on April 14, 2005 is acknowledged.

Claims 1-6, 10, 11, 20-23, 25-29, 32-34, 37-44, 47, and 48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Election was made **without** traverse in the reply filed on April 14, 2005.

Applicant's election with traverse of the species of SEQ ID NO:2 in the reply filed on April 14, 2005 is acknowledged. The traversal is on the ground that there is no burden to examine all the peptide species encompassed by the generic peptide sequence of SEQ ID NO:1. Upon examination of the prior art, the search has been extended beyond the elected species of SEQ ID NO:2 to include SEQ ID NO:10, the other sequence contained within the genus sequence of SEQ ID NO:1.

Information Disclosure Statement

2. The IDS received July 18, 2003 is acknowledged and considered. The International Search Report and International Preliminary Examination Report for PCT/NL98/00424 have been considered but they have been lined through because it is inappropriate to list such documents on an IDS.

Specification

3. Applicant is thanked for the amendments to the specification received January 5, 2004 that insert appropriate SEQ ID numbers next to the disclosed sequences in the text of the specification, including the Brief Descriptions of the Figures.

The disclosure is objected to because of the following informalities:

A) The brief description of Figures 5, 6, 7 and 8 contain symbols that do not correspond to the symbols actually used in the graphs presented in said Figures.

B) The brief description of Figure 12 makes references to the colors red and green, which are not distinguishable in black and white. As such it is difficult to understand the data being presented in Figure 12.

C) Line 2 of page 37 contains a formatting error in that the Greek symbol β appears as b.

D) The specification contains an embedded hyperlink and/or other form of browser-executable code on page 53, line 20. Applicant is required to delete

the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

E) Tables 3-6 include sequence information that is not identified by a SEQ ID number. See 37 CFR 1.821-1.825.

F) The legend to Tables 4 and 5 indicate that some amino acid residues are represented in bold text, but the Tables as currently presented do not appear to contain any bold text.

Appropriate correction of all of the above is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claims 7-9, 12-19, 24, 30, 31, 35, 36, 45, 46, 49, and 50 are objected to because they depend from withdrawn claims. Amendment of base claim 7 to include all the limitations currently recited in withdrawn claims 1 and 4 would remove this objection.

Claim Rejections - 35 USC § 112

4. Claims 7, 12-19, 30, 31, 35, 36, 45, and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Base claim 7 recites a method for inducing tolerance in a transplant recipient subject by administering an HA-1 peptide to said subject. As such, any process steps that occur after administration of the peptide must occur *in vivo*. Since the method practitioner cannot control the fate of the administered peptide once it has been administered, any subsequent method steps are inherent properties of the administration of the HA-1 peptide. Dependent claims 12-19, 30, 31, 35, 36, 45 and 46 add the limitations that cytotoxic t-lymphocytes (CTL) are generated by the method of claim 7, an *in vivo* method. Tolerance, as defined by Janeway et al. Immunobiology, 5th edition on page 705, is "[T]he failure to respond to an antigen; the immune system is said to be tolerant to self antigens." If CTL are elicited by the administration of a HA-1 peptide, a response to an antigen (i.e. the HA-1 peptide) has occurred and thus tolerance has not been achieved. Applicant's specification does not appear to disclose any examples, mechanism, or discussion of how an administered HA-1 peptide induces both tolerance and CTL generation *in the same individual.* As such, the scope of the

claims has been broadened beyond that which was disclosed in the specification. Such a broadening is new matter.

5. Claims 7-9, 12-19, 24, 30, 31, 35, 36, 45, 46, 49, and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Base claim 7 recites a method of treatment for various conditions by administering an HA-1 peptide. As such, any process steps that occur after administration of the peptide must occur *in vivo*. Since the method practitioner cannot control the fate of the administered peptide once it has been administered, any subsequent method steps are inherent properties of the administration of the HA-1 peptide. Dependent claims 12-19, 31, 35, 36, 45 and 46 add the limitations that CTL are generated by the method of claim 7, an *in vivo* method. Tolerance, as defined by Janeway et al. Immunobiology, 5the edition, is "[T]he failure to respond to an antigen; the immune system is said to be tolerant to self antigens." (see page 705 of Janeway et al.). If CTL are elicited by the administration of a HA-1 peptide (or by administration of a tumor cell that presents the peptide as in claims 31, 45, and 46), a response to an antigen (i.e. the HA-1 peptide) has occurred and thus tolerance has not been achieved. Applicant's specification does not appear to disclose any examples, mechanism, or discussion of how an administered HA-1 peptide induces both tolerance and CTL

generation *in the same individual*. As such, it is not possible for the same method to induce tolerance and induce the generation of CTL. It is noted that some of the dependent claims appear to indicate that the CTL are generated *in vitro* or *ex vivo*, which does not appear to make logical sense, since as has been already indicated, base claim 7 requires that the HA-1 peptide be administered to the patient, thus making it, and claims that depend from it, *in vivo* methods of treatment.

The term "tolerance" does not appear to be clearly defined by the specification, so the examiner has used the above definition provided by Janeway et al. Tolerance is a broad concept that includes ideas such as clonal deletion, clonal inactivation, anergy, immunological ignorance, immune deviation, and immune suppression, all of which can be directed to both B and T lymphocytes (Janeway et al., pages 523-546, particularly the middle paragraph of page 533 and page 546). Applicant's specification does not present data demonstrating the occurrence of all of these phenomena in conjunction with the HA-1 peptides of the present invention, but rather confines its discussion to the use of HA-1 peptides that bind MHC molecules and are presented to T cells to treat transplant rejections and GvHD. As such, the specification does not provide guidance or working example concerning the use of HA-1 peptides that encompasses the entire scope of the term tolerance.

The various conditions recited in claim 7 that are treated by administration of an HA-1 peptide as disclosed in the specification include the prevention of tissue transplant rejection and/or Graft versus Host disease (GvHD), or the treatment of an autoimmune disease. The specification provides information on how the minor histocompatibility

antigen (mHag) HA-1 acts as a barrier to organ and tissue transplantation, but the specification does not appear to indicate either through working examples or discussion, that recognition of HA-1 is involved in any autoimmune disease (note that transplantation is not an autoimmune disease since the transplanted material is not "self".) As such, a skilled artisan would not be able to treat patients suffering from autoimmune diseases by administering HA-1 peptides without conducting additional experimentation. The results of such experimentation are unpredictable due to the large number of antigenic molecules recognized in typical autoimmune diseases (Bach et al., Immunological Reviews, (1998) 164:139-155, see entire document, particularly the abstract).

Claim 7 recites that transplant rejection and/or GvHD is prevented by the administration of HA-1 peptides to the graft recipient. It is known in that art that mHag other than HA-1 exist, and that mHag are capable of inducing vigorous immune responses that lead to graft rejection or GvHD (Goulmy et al., reference C7 on the IDS submitted July 18, 2003, see entire document, particularly the paragraph that spans the left and right columns of page 180). The disclosure indicates that a significant percentage of transplant rejection and GvHD reactions in HLA-matched transplantation settings are directed to HA-1. However, the data does not indicate that HA-1 is the only immunological target that is recognized in all transplant rejections and GvHD reactions, so even if Applicant's method is successful in stopping immune reactions directed to HA-1, immune reactions to other mHags will occur. Since transplant rejection or GvHD can still occur due to the presence of other mismatched mHags, Applicant's method

cannot truly prevent the occurrence of transplant rejection or GvHD. Additionally, the claims do not recite that the patient being administered an HA-1 peptide has received or will be receiving a tissue or organ graft that is HLA matched. Immune reactions directed to HLA molecules are dominant to those directed toward mHags in transplantation settings (hence the "minor" in mHag) and if the graft is not HLA matched, administration of the HA-1 peptides disclosed in the specification will not have any therapeutic benefit.

The specification discloses that two alleles of HA-1 are known to exist in the human population, said alleles differing by the presence of a single amino acid (see particularly page 36, lines 8-24 and Den Haan et al., citation C5 on the IDS submitted July 18, 2003). This amino acid polymorphism is located within the peptide sequence consisting of SEQ ID NO:1, with the two possible sequences disclosed as SEQ ID NO:2 which has an H at position 3 (the HA-1^H allele, VLHDDLLEA) and SEQ ID NO:10 which has an R at position 3 (the HA-1^R allele, VLRDDLLEA). The GvHD associated mHag HA-1 is due to the recognition of the HA-1^H peptide presented on host cells by graft CTL (see particularly from line 7 of page 37 to line 21 of page 39). The peptides of SEQ ID NO:1 are disclosed as binding to HLA-A2.1 (see particularly from line 9 of page 6 to line 10 of page 7). Residues 1-6 of SEQ ID NO:1 (and hence the HA-1 polymorphism) are disclosed as being contained within a 9 amino acid peptide sequence that binds HLA-B60 (see particularly from line 27 of page 22 to line 11 of page 23). The specification defines a peptide of the invention on page 20, lines 5-22, as being at least 7 amino acids but no more than 15 amino acid residues that contains the HA-1 polymorphism and is capable of being presented on MHC class I or class II molecules. It should be

noted that it is not disclosed that any HA-1 peptide of the indicated length containing the polymorphism either does bind an MHC class II molecule or is even predicted to bind an MHC class II molecule.

The claims as currently written do not require that the patient to whom an HA-1 peptide is administered express either HLA-A2.1 or -B60. Attempts to identify peptides that bind other HLA molecules, such as HLA-A1, -A11, -A24, -B7, -B8, -B14, -B35, and –B62, and that comprise the polymorphism in HA-1 were not successful (see particularly lines 1-4 of page 56 and Table 3). If a patient does not express an HLA allele capable of binding an HA-1 peptide of the instant invention, Applicant's claimed method will not work. Data presented by Applicant appears to indicate that HA-1 peptides of the instant invention can strongly bind only HLA-A2.1 and -B60 and can weakly bind -A3. As such, only patients who express HLA-A2.1, -B60 and possibly -A3 can potentially be treated by Applicant's method. No data or working examples are presented to indicate that administration of the HA-1 peptides of the instant invention is therapeutically useful in treating transplant rejections or GvHD.

The HA-1 peptides of the instant invention, in addition to being between 7 and 15 amino acids long and encompassing the polymorphism present in HA-1, also include derivatives that have similar function. Derivative peptides can contain substituted amino acids, and similar function means "that at least one of the properties and/or activity is the same in kind, not necessarily in amount, as compared to the functional or immunological properties and/or activity of the peptide the analog or derivative is derived from" (see particularly lines 4-8 of page 24). As such, derivative HA-1 peptides

can be agonists, antagonists, peptide-like or peptidomimetic, and include altered peptide ligands (APL) (see particularly page 6, lines 27-29, and from line 29 of page 9 to line 16 of page 10). The specification does not provide any guidance or working examples using derivatives or analogs of HA-1 peptides as antagonists the activity of a T cell recognizing an HA-1 peptide, nor does it appear to provide any guidance on which residues of the HA-1 peptide should be modified to generate antagonist peptides. Further, Goulmy teaches that the use of a single TCR antagonist specific for a minor histocompatibility antigen such as HA-1 is of questionable value due to the potential number of MHC molecules that must be targeted in the population and due to the presence of additional responses to other mHags (Immunological Reviews, (1997) 157:125-140, see entire document, particularly the lower third of the left column of page 134). As such a skilled artisan would not be able to make or use HA-1 antagonist peptides without conducting additional unpredictable experimentation based upon the teachings of Goulmy et al.

Applicant has indicated that tolerance can be induced by administration of HA-1 peptides in very small doses intravenously, or in large doses orally, or through other routes of administration (see particularly page 7, lines 24-28 and page 10, lines 13-14). Applicant states that in all forms of transplantation, the HA-1 peptide is used to induce tolerance in HA-1 negative recipients (see page 10, lines 14-16). As discussed above, it appears that only the HA-1^H allele is recognized by CTL, yet the term HA-1 peptide as used by Applicant appears to include the HA-1^H and HA-1^R alleles as well as derivatives such as altered peptide ligands. Graft material taken from HA-1^R donors and

transferred to HA-1^H recipients initiates GvHD, so the presence of the HA-1^R peptide in the donor does not in any way induce tolerance of the donor cells to recipient cells expressing the HA-1^H peptide. It also seems unlikely that administration of the HA-1^R peptide to HA-1^H recipients before transfer of either HA-1^H or HA-1^R donor material will have any therapeutic effect. The administered peptide cannot possibly displace all of the HA-1^H peptides expressed on the recipient's cells to prevent CTL recognition by HA-1^R graft material, and HA-1^H graft material is not mismatched in a HA-1^H host since the graft is already "tolerant" to HA-1^H. As such, it is not clear how administration of a peptide comprising HA-1^R (SEQ ID NO:10) to any individual will be therapeutically useful since CTL do not recognize this structure. Peptides comprising HA-1^H (SEQ ID NO:2) would likely stimulate the production of CTL since this allele is recognized by CTL, and indeed some of Applicant's disclosed methods are designed to generate CTL. As discussed above, any method that generates CTL cannot be considered a method of inducing tolerance. It should be noted that the claims as currently recited indicate that the patient to whom a peptide of the instant invention is administered is the recipient of a tissue graft. The specification does not appear to indicate why it would be desirable to induce the formation of CTL in the graft recipient. The specification does indicate that the way in which a peptide is administered (dosage, route etc...) can make a stimulatory peptide into a toleragenic peptide, but such information is not recited in the claims. Further, no working examples are provided to show that different effects (tolerance versus CTL generation) can be achieved by some differential form of peptide administration.

Therefore, based upon the lack of guidance or working examples concerning how administration of a HA-1 peptide to the same individual can simultaneously induce tolerance and a CTL response, the lack of guidance or working examples concerning the use of HA-1 peptides that encompass the full scope of the term tolerance, the lack of guidance or working examples concerning the role of HA-1 in autoimmune diseases, the inability to prevent transplant rejection and GvHD by administration of an HA-1 peptide since other mHags also contribute to transplant rejection and GvHD, the inability to prevent transplant rejection and GvHD by administration of an HA-1 peptide since not all patients receiving grafts express the appropriate MHC class I molecules HLA-A2.1 and –B60, the lack of guidance or working examples concerning how to generate antagonists of the HA-1 peptides of the present invention, the prior art teachings that treatment with antagonists to a single mHag such as HA-1 would not be effective due to the need of the antagonist to bind multiple MHC molecules across the patient population and due to the presence of other mHags to which immune responses are also directed that result in transplant rejection or GvHD, and because it is unclear how administration of the genus of products disclosed as HA-1 peptides will induce tolerance in all individuals, a person of skill in the art would be unable to make or use Applicant's claimed method of treatment without first conducting additional research.

6. Claims 7-9, 12-19, 24, 30, 31, 35, 36, 45, 46, 49, and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of the peptides disclosed as SEQ ID NO:1 in the instant invention.

Applicant is not in possession of all analogs and derivatives of the peptide of SEQ ID NO:1.

Applicant has claimed a method of administering a genus of HA-1 peptides that includes analogs and derivatives. A particular HA-1 peptide is identified as SEQ ID NO:1, and its two possible subsequences (SEQ ID NO:2 and SEQ ID NO:10) are disclosed as binding HLA-A2.1 and being useful for the induction of tolerance in the treatment of transplant rejection and GvHD. The specification also discloses other HA-1 peptide sequences that bind the HLA-B60 molecule and have similar utility. The specification defines a peptide of the invention on page 20, lines 5-22, as being at least 7 amino acids but no more than 15 amino acid residues that contains the HA-1 polymorphism. Derivatives and analogs are indicated as being of the same or different length, agonists, antagonists, peptide-like, or peptidomimetic that have the same or at least similar functional immunological properties or activity (see particularly lines 23-29 of page 6 of the specification). As such, it is not clear if analogs and derivatives are limited to a length of 7 to 15 amino acids, or if analogs and derivatives can be longer and/or shorter sequences. Functional properties of HA-1 peptides of the invention that appear to be disclosed include binding to either HLA-A2.1 or –B60 and the ability to be recognized by the TCR of a CTL when presented in the context of MHC class I

molecules. Guidance or examples of the structure of analogs and derivatives of HA-1 peptides does not appear to be contained within the specification, nor does there appear to be guidance as to what structure(s) of the HA-1 peptide must be maintained by analogs and derivatives that allow for binding to MHC molecules and recognition by CTL. As such, applicant has failed to adequately disclose what would be required for a molecule to be recognized by a skilled artisan as a analog or derivative of an HA-1 peptide since the structure required HA-1 peptide analogs and derivatives is not disclosed. Thus, Applicant was not in possession of the claimed genus of all HA-1 peptides, analogs, and derivatives. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. No claims are allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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